REGULATION OF INTRACELLULAR GLUCOCORTICOID CONCENTRATIONS

This invention relates to the interconversion of inactive 11-keto steroids with their active 11β-hydroxy equivalents, to methods by which the conversion of the inactive to the active form may be controlled, and to useful therapeutic effects which may be obtained as a result of such control. More specifically, but not exclusively, the invention is concerned with interconversion between cortisone and cortisol in humans.

Glucocorticoids such as cortisol have a number of diverse effects on different body tissues. For example, the use of cortisol as an anti-inflammatory agent was described in our International Patent Application WO 90/04399, which was concerned with the problem that therapeutically administered cortisol tends to be converted in the body to inactive cortisone by 11β-hydroxysteroid dehydrogenase enzymes. Our earlier invention provided for the potentiation of cortisol by the administration of an inhibitor of the 11β-dehydrogenase activity of these enzymes.

Another major physiological effect of cortisol is its antagonism to insulin, and it is known for example that high concentrations of cortisol in the liver substantially reduce insulin sensitivity in that organ, thus tending to increase gluconeogenesis and consequently raising blood sugar levels [1]. This effect is particularly disadvantageous in patients suffering from impaired glucose tolerance or diabetes mellitus, in whom the action of cortisol can serve to exacerbate insulin resistance. Indeed, in Cushing's syndrome, which is caused by excessive circulating concentrations of cortisol, the antagonism of insulin can provoke diabetes mellitus in susceptible individuals [2].

As mentioned above, it is known that cortisol can be converted in the body to cortisone by the 11β-dehydrogenase activity of 11β-hydroxysteroid dehydrogenase enzymes. It is also known that the reverse reaction, converting inactive

--**REFERENCE TO RELATED APPLICATIONS**

This application is a divisional application of ~~allowed~~ U.S. ~~Application Serial No.~~ 09/029,535, filed February 27, 1998, which is the National Stage application of international application PCT/GB96/02134 filed August 28, 1996, published as WO 97/07789 on March 6, 1997, and claims priority from British Application 9517622.8 filed August 29, 1995. Reference is made to U.S. Application Serial No. 10/061,044 filed January 30, 2002 as a divisional of U.S. ~~Application Serial No. 09/029,535~~. Reference is also made to four additional applications, also filed as divisional applications of U.S. ~~Application Serial No. 09/029,535~~ on February 22, 2002, application numbers ~~to be assigned, (Attorney docket numbers 674543-2001.2, 674543-2001.3, 674543-2001.5 and 674543-2001.6)~~.

The above-mentioned applications, as well as all documents cited herein and documents referenced or cited in documents cited herein, are hereby incorporated herein by reference.--

IN THE CLAIMS:

Kindly cancel claims 1-13, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

Kindly add new claims 14 and 15, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents:

--14. (New) A method for determining whether a compound or composition is a regulator of intracellular glucocorticoid activity in adipose tissue comprising determining whether said compound or composition inhibits reductase activity of 11-Beta-hydroxysteroid dehydrogenase 1 (11-Beta HSD1) in said tissue.

15. (New) The method of claim 1, wherein determining whether said compound or composition inhibits reductase activity of 11-Beta HSD1 comprises:

obtaining reductase activity of 11-Beta HSD1 in an isolate *in vitro* adipocyte cell population, and

contacting said compound or composition with said adipocyte cell population.--

IN THE ABSTRACT:

Please accept the enclosed page entitled "Abstract".

potential beneficial effects of inhibitors of 11β-reductase are many and diverse, and it is envisaged that in many cases a combined activity will be demonstrated, tending to relieve the effects of endogenous glucocorticoids in diabetes mellitus, obesity (including centripetal obesity), neuronal loss and the cognitive impairment of old age. Thus, in a further aspect, the invention provides the use of an inhibitor of 11β-reductase in the manufacture of a medicament for producing multiple therapeutic effects in a patient to whom the medicament is administered, said therapeutic effects including an inhibition of hepatic gluconeogenesis, an increase in insulin sensitivity in adipose tissue and muscle, and the prevention of or reduction in neuronal loss/cognitive impairment due to glucocorticoid-potentiated neurotoxicity or neural dysfunction or damage.

From an alternative point of view, the invention provides a method of treatment of a human or animal patient suffering from a condition selected from the group consisting of: hepatic insulin resistance, adipose tissue insulin resistance, muscle insulin resistance, neuronal loss or dysfunction due to glucocorticoid potentiated neurotoxicity, and any combination of the aforementioned conditions, the method comprising the step of administering to said patient a medicament comprising a pharmaceutically active amount of an inhibitor of 11β-reductase.

As mentioned previously, the factors which control the relative activities of 11β-dehydrogenase and 11β-reductase in different conditions, especially by the 11β-HSD1 isozyme, are poorly understood. It is likely that an 11β-reductase inhibitor will be selective for the 11β-HSD1 isozyme *in vivo*. We have found, for instance, that glycyrrhetinic acid (a known inhibitor of 11β-dehydrogenase) has no effect on 11β-reductase *in vivo* [26]. However, we have surprisingly found that carbenoxolone, which is known as an inhibitor of the 11β-dehydrogenase enzyme, also inhibits 11β-reductase *in vivo* [26,27]. In preferred embodiments, therefore, the